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Prunus armeniaca hydroxynitrile lyase (*ParsHNL*)-catalyzed asymmetric synthesis of cyanohydrins from sterically demanding aromatic aldehydes

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ABSTRACT

Herein we report the biocatalytic asymmetric synthesis of cyanohydrins by using a new (*R*)-HNL from *Prunus armeniaca*. Several sterically demanding aromatic aldehydes which have never been used as substrates for any known HNLs are employed for the new (*R*)-HNL from *P. armeniaca*. The cyanohydrins synthesized are obtained in good chemical yield with excellent enantioselectivities.

1. Introduction

Hydroxynitrile lyases (HNLs) are one of the key enzymes in cyanogenic plants, catalyzing the final step in the biodegradation pathway of cyanogenic glycosides releasing HCN and the corresponding carbonyl components.[1] There exist four different types of HNL (EC. No. 4.1.2.10; 4.1.2.11; 4.1.2.37 and 4.1.2.39), among them mandelonitrile lyase (4.1.2.10) is only (*R*)-selective [i.e., it accepts (*R*)-mandelonitrile as its natural substrate] whereas rest are (*S*)-selective. (*R*)-Selective hydroxynitrile lyases found from different plant species are quiet similar in their enzymatic properties (molecular weight distribution, sequence homology and reactive properties).[2] Enantiomerically pure cyanohydrins have attracted the attention of organic chemists, as well as enzymologists, due to their potential as chiral building blocks and interesting biological properties. Enantiopure cyanohydrins serve as intermediates for several industrially useful chemicals; the use of chiral cyanohydrins as building blocks for the production of important chemicals is likely to continue growing, as it avoids problems associated with the resolution of or asymmetric synthesis of certain products.[3] One of the most promising and interesting ways to enantiomerically pure cyanohydrins is the HNL-catalyzed addition of a cyanide source to the respective carbonyl compounds.[4] HNLs are now widely used as efficient biocatalysts for the asymmetric synthesis of various cyanohydrins. The resulting cyanohydrins are versatile intermediates for a broad variety of chiral synthons. The reaction is important from an organic chemists point of view, as it allows the synthesis of enantiomerically pure compounds from pro-stereogenic substrates in quantitative yield.

In general it has been observed that HNL from *Rosaceae* species (almond, plum, cherry and peach) exhibits broad levels of substrate acceptance (aliphatic, aromatic), whereas HNL from cassava (*Manihot esculenta*) and rubber tree (*Hevia brasilinesis*) are only selective towards aliphatic or aromatic substrates.[3] In a true sense of chemical reactivity HNL from almond (*Prunus amygdalus*), Japanese apricot (*Prunus mume*) shows excellent substrate (saturated aliphatic aldehydes, unsaturated aliphatic aldehydes, aromatic aldehydes, heteroaromatic aldehydes, methyl ketones and cyclic ketones) tolerance over other species for the asymmetric synthesis of the corresponding cyanohydrins.[5] Herein we report our findings on the biocatalytic cyanohydrin formation by a new (*R*)-HNL, *ParsHNL* (*P. armeniaca*, white apricot, shakarpara cultivar) from polycyclic aromatic aldehydes and aromatic aldehydes with bulky substitution.

2. Results and discussion

Recently we found a new (*R*)-HNL from white apricot (shakarpara cultivar, found in the himalayan region of Nepal and India; *P. armeniaca*). The new enzyme (*ParsHNL*) exhibits excellent enantioselectivity for the preparation of several cyanohydrins from aliphatic and aromatic carbonyl compounds.[6] Recently we have synthesized several δ,ε-unsaturated cyanohydrins by using *ParsHNL* from the corresponding γ,δ-unsaturated aldehydes with excellent enantioselection.[7] At this point we thought that it would be appropriate to use the new enzyme *ParsHNL* for the asymmetric biocatalytic synthesis of several cyanohydrins from various aldehydes, which have been never tested as HNL substrates with all the known HNLs existing in the literature. We chose different polycyclic aromatic aldehydes and substituted aromatic aldehydes for the substrate of *ParsHNL*-catalyzed cyanohydrin formation (Scheme 1).

We generally applied vigorously stirred biphasic reaction media (diisopropyl ether/aq Na-citrate buffer, pH 4.0) to the biocatalytic cyanation reaction for substrates **1**–**11**, freshly generated HCN was used as the cyanating source. When 4-biphenyl carboxaldehyde (Substrate **1**) was used as a substrate for *ParsHNL*-catalyzed hydrocyanation reaction, the respective cyanohydrin was obtained with excellent selectivity (yield: 78% and ee: 96%). On the other

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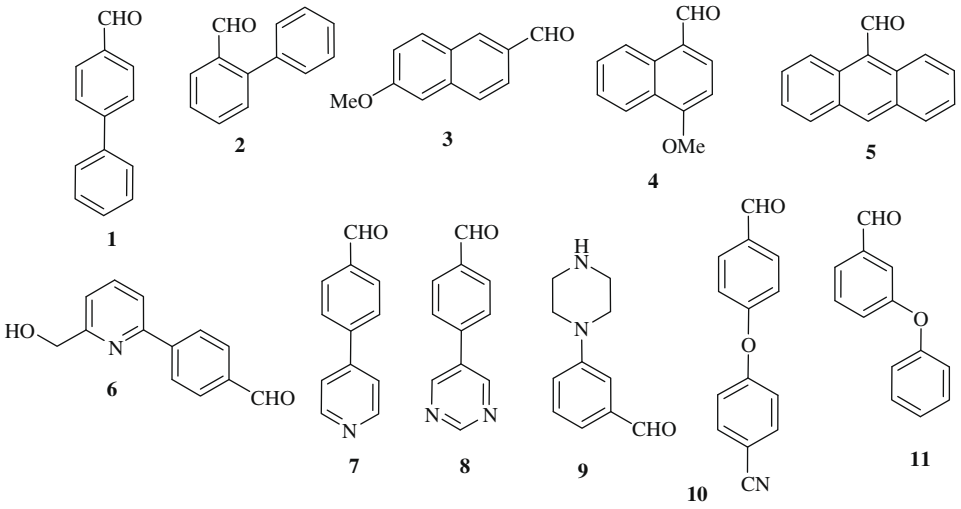


Scheme 1. Potential *ParsHNL* substrates for asymmetric cyanohydrin formation.

hand, when a structurally similar 2-biphenyl carboxaldehyde (Substrate **2**) was subjected to *ParsHNL*-catalyzed hydrocyanation, the respective cyanohydrin was obtained with low enantioselection (ee: 32%). A similar trend with *ortho*-substituted aromatic aldehydes has already been pointed out and it was observed that, the presence of substituents at the *ortho*-position (irrespective of their electronic nature) always lead to sluggish reactions (poor ee) compared to *meta*- and *para*-substituents.[5a] Next we attempted *ParsHNL*-catalyzed hydrocyanation reaction of two polycyclic aromatic aldehydes **3** and **4**. HNL-catalyzed hydrocyanation (*PaHNL, P. amygdalus,* almond seed) of aromatic polycyclic aldehydes, for example, 1-naphthaldehyde and 2-naphthaldehyde were reported earlier by Cruz Silva et al.,[8] with excellent stereoselectivity was observed for the synthesized cyanohydrins. When we have attempted *ParsHNL*-catalyzed cyanohydrin formation of 6-methoxy-2-naphthaldehyde (Substrate **3**) and 4-methoxy-1-naphthaldehyde (Substrate **4**), the respective cyanohydrins were obtained with excellent enantioselectivities (Table 1) and good chemical yields. This was not true in the case of 9-anthracenecarboxaldehyde (Substrate **5**). When substrate **5** is subjected to the *ParsHNL*-catalyzed hydrocyanation reaction, the cyanohydrin is obtained in good chemical yield, but the cyanohydrin is racemic. It is obvious that the enzyme plays a small role in the outcome of this reaction product; chemical cyanation prevails over a biocatalytic reaction and the cyanohydrin obtained is purely racemic in nature. When we attempted a biocatalytic hydrocyanation reaction of 9-anthracene carboxaldehyde with *PaHNL*, the respective cyanohydrin was also obtained as a racemic mixture. Hence we can conclude that (*R*)-HNL from *prunus* species in its active site can accommodate polycyclic aromatic aldehydes having two fused aromatic rings only, extra substituents in those aromatic rings are also well accepted by the enzymes (Substrates **3** and **4**).

Table 1
ParsHNL-catalyzed hydrocyanation of several aldehydes

Aldehydes	Reaction time (h)	Yield (%)	Ee[a] (%)
1	8	72	96
2	8	68	32
3	7	70	97
4	8	68	94
5	10	78	0
6	8	74	98
7	10	74	96
8	12	78	94
9	9	72	96
10	8	80	96
11	6	82	99[b]

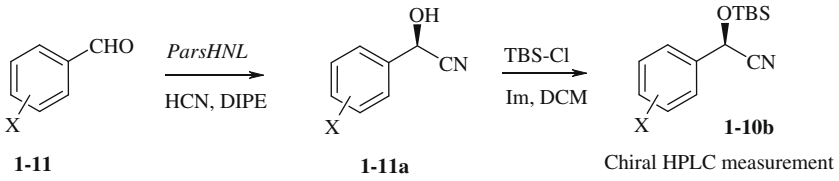
[a] Ee was determined by chiral HPLC (CHIRALCEL-OJ H; hexane: 2-PrOH; flow rate 0.5–1 ml/min) measurement of the -OTBS ethers of the cyanohydrins.
[b] This cyanohydrin itself is well resolved using HPLC under the experimental condition.

Next we attempted *ParsHNL*-catalyzed hydrocyanation of aldehydes **6**–**10**, where the aromatic aldehyde is substituted either at the *meta* or *para* position by a bulky phenyl, pyridyl, pyrimidinyl and related groups. Substrates **6** and **7** can be considered as *para* substituted benzaldehyde mimic, where a pyridyl group is present at the *para* position. It is known that pyridine-2-carboxaldehyde and pyridine-4-carboxaldehyde are not good substrates for (*R*)-HNL isolated from *prunus* species. As these aldehydes are highly activated, the corresponding competing chemical cyanation reaction causes lowering of the enantioselection for the cyanohydrins synthesized.[5] However for substrates **6** and **7** the aldehyde functionality and the pyridine nucleus are not part of the same aromatic ring, both the substrates provide excellent enantioselection for the respective cyanohydrins. For substrate **8**, a pyrimidinyl ring is introduced at the *para*-position of the benzaldehyde. The respective cyanohydrin from compound **8** is obtained with good chemical yield (78%) and with 94% enantioselection. In substrate **9**, the benzaldehyde is substituted by a piperazinyl group at the *meta* position. Compound **9** yields the respective cyanohydrin in 72% yield with 96% enantioselection after biocatalytic hydrocyanation with *parsHNL*. For compounds **10** and **11**, the benzaldehyde is substituted at the *para* and *meta* position by phenoxy groups and both the substrates provide excellent results in terms of chemical yield and enantioselection for their respective cyanohydrins. Substrate **11**, 3-phenoxybenzaldehyde, was used as a substrate for the first time with this type of HNL from *prunus* species, for example, *ParsHNL* which yields the respective cyanohydrin in 82% yield and with 99% enantioselection. The cyanohydrin obtained from 3-phenoxybenzaldehyde served as an advanced intermediate for synthetic pyrethroids such as cypermethrin and deltamethrin.

The enantioselectivity of all the cyanohydrins are determined by chiral HPLC measurement of their respective-OTBS (*tert*-butyldimethyl silyl; di-OTBS ether in the case of **6** and **9**, Scheme 2) ethers.

3. Conclusion

In conclusion the present study demonstrates that *ParsHNL* is capable of catalyzing a biocatalytic hydrocyanation reaction of various structurally unique aromatic aldehydes with HCN. Although



Scheme 2. Enzymatic hydrocyanation reaction and derivatization of the cyanohydrins.

the enzyme is relatively new, it exhibits excellent substrate acceptance in terms of chemical yield and enantioselection for the synthesized cyanohydrins. Many of the substrates, which act as very good HNL substrates, are reported for the first time in this article. Further studies on the synthetic potential of the new enzyme system *ParsHNL* are currently in progress in our laboratory.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. Ripened white apricot (shakarpara, *P. armeniaca*) was obtained from local fruit market in Shimla (Himachal Pradesh, India) in the month of June, 2008 and was stored at 4 °C. All aldehydes used in the experiment are freshly distilled or washed with aq $NaHCO_3$ solution to minimize the amount of free acid, which is supposed to inhibit HNL activity. Mandelonitrile and acetone cyanohydrins were freshly distilled prior to use. Reactions were monitored by TLC, carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 400 MHz spectrometer at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Chiral HPLC was performed using chiral OJ-H column (0.46 × 25 cm, Daicel industries) with Shimadzu Prominence 20AT and UV–vis detector (254 nm). Eluting solvent used was different ratios of hexane and 2-propanol.

4.2. Enzyme extraction from *P. armeniaca* (shakarpara apricot)

Ripened fruits were taken and the fleshy cover was removed to obtain the seeds. The upper layers of the seeds were cracked with hammer to give the soft kernels inside. Those kernels were collected and homogenized in a homogenizer at 4 °C, with aq potassium phosphate buffer (10 mM, pH 6.0), to give a milky suspension. The suspension was filtered through four layers of cheese cloth to remove the insoluble part. After this it was centrifuged (18,800*g*, 30 min), removal of the residue gives a crude preparation of HNL. The crude preparation was fractionated with $(NH_4)_2SO_4$. Proteins precipitating with 30% saturation were collected by centrifugation (18,800*g*, 20 min), dissolved in the minimum volume of phosphate buffer and dialyzed against the same buffer with three changes. After this the dialyzed solution was centrifuged and the supernatant was stored at 4 °C and assayed for HNL activity.

4.3. *ParsHNL* assay

In a typical assay reaction, 1.0 M of benzaldehyde solution (in DMSO, 40 μL) was dissolved in 400 mM citrate buffer (760 μL, pH 4.0), followed by the addition of 100 μL of enzyme solution and 100 μL of 1.0 M NaCN solution (total reaction volume 1 mL), and the reaction mixture was incubated in a rotary shaker. After 5 min, the 100 μL of the reaction mixture was taken out and extracted with 900 μL hexane/2-propanol (9:1), the organic layer was analyzed with chiral HPLC for the formation of (*R*)-mandelonitrile. A blank reaction was also performed without enzyme, and the amount of mandelonitrile obtained was deducted from the biocatalyzed reaction product. One unit of the enzyme is defined as the amount of the enzyme that produces 1 mmol of (*R*)-mandelonitrile under the reaction conditions in 1 min. The protein content in all the HNL was measured by the Bradford method using Bio-Rad protein assay kit using BSA as the standard.

4.4. Preparation of racemic cyanohydrin-TBDMS ethers for HPLC standard

Normally, an aqueous solution of NaCN (3–5 equiv) in water is added to a solution of the carbonyl compounds (1 equiv) in acetic acid. After completion of reaction (as indicated by TLC), the reaction mixture was neutralized with an aq $NaHCO_3$ solution. Then it was extracted with ether and dried (anhydrous Na_2SO_4). Evaporation and purification by column chromatography on silica afforded the cyanohydrins in good yield. Racemic cyanohydrins obtained by this method are taken in dry DCM (dichloromethane) followed by the addition of imidazole (3 equiv) and TBDMS-Cl (3 equiv). The reaction mixture was stirred overnight at room temperature. After completion of the reaction (indicated by TLC) it was evaporated and purified by chromatography to yield the cyanohydrin-TBDMS ethers which were fully characterized by NMR spectroscopy and used for HPLC standard.

4.5. General procedure for synthesis of cyanohydrins by *ParHNL*

To a solution of aromatic aldehydes **1**–**10** in DIPE, a solution of *ParsHNL* (300 IU/mmol of aldehyde, DIPE/enzyme; 1:1 v/v) was added and the resulting mixture was stirred vigorously until an emulsion was formed. The pH of the enzyme solution was previously adjusted to 4.0 with 10% citric acid solution. Freshly prepared HCN in DIPE (2 equiv) was added to it, and the temperature of the solution was maintained at 10 °C. After completion of the reaction it was extracted thoroughly with ether several times and the organic layer was dried (Na_2SO_4). Evaporation of the solvent yielded the crude cyanohydrins which were purified by chromatography.

4.6. Preparation of HCN in DIPE

A first, NaCN (10 g) and citric acid (0.1 g) were dissolved in water (100 mL). The solution was cooled in an ice/water bath and extracted with DIPE (50 mL), while acidifying with 33% HCl until pH 5.5. The water layer, which contained a suspension of NaCl, was extracted twice with DIPE (25 mL). The combined DIPE layers were stored in a dark bottle. The above procedure must be performed in a well-ventilated fume hood with proper glass ware and safety precautions.

4.7. (*R*)-Biphenyl-4-yl-(*tert*-butyl-dimethyl-silanyloxy)-acetonitrile 1b

δ_H: 0.18 (s, 3H), 0.26 (s, 3H), 0.91 (s, 9H), 5.57 (s, 1H, C*H*–CN), 7.2–7.6 (m, 9H, Ar-*H*). δ_C: −5.0, −5.1, 18.24, 25.6, 63.87, 119.27, 126.6, 127.19, 127.67, 127.74, 128.9, 135.46, 140.3, 142.3. Elemental Anal. Calcd for $C_{20}H_{25}NOSi$: C, 74.25; H, 7.79; N, 4.33. Found: C, 74.20; H, 7.83; N, 4.35. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 19/1, flow rate = 0.8 mL/min) t_R = 10.56 min (major, *R*), t_R = 11.8 min (minor, assumed *S*).

4.8. (*R*)-Biphenyl-2-yl-(*tert*-butyl-dimethyl-silanyloxy)-acetonitrile 2b

δ_H: −0.11 (s, 3H), 0.014 (s, 3H), 0.83 (s, 9H), 5.45 (s, 1H, C*H*–CN), 7.2–7.35 (m, 3H, Ar-*H*), 7.4–7.55 (m, 5H, Ar-*H*), 7.7 (d, *J* = 6.0 Hz, 1H, Ar-*H*). δ_C: −5.42, −5.37, 17.96, 25.4, 61.14, 119.71, 127.66, 127.87, 128.29, 128.52, 129.07, 129.13, 129.95, 134.5, 139.19, 140.5. Elemental Anal. Calcd for $C_{20}H_{25}NOSi$: C, 74.25; H, 7.79; N, 4.33. Found: C, 74.26; H, 7.85; N, 4.32. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 99/1, flow rate = 0.5 mL/min) t_R = 8.02 min (major, *R*), t_R = 8.79 min (minor, *S*).

4.9. (*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-(6-methoxy-naphthalen-2-yl)-acetonitrile 3b

δ_H: 0.14 (s, 3H), 0.23 (s, 3H), 1.0 (s, 9H), 3.94 (s, 3H), 5.64 (s, 1H, C*H*–CN), 7.1–7.3 (m, 2H, Ar-*H*), 7.5 (m, 1H, Ar-*H*), 7.6-7.8 (m, 3H, Ar-*H*). δ_C: −4.23, −4.16, 19.06, 26.42, 56.2, 65.14, 106.65, 120.22, 120.42, 124.99, 126.24, 128.67, 129.26, 130.56, 132.43, 135.75, 159.31. Elemental Anal. Calcd for $C_{19}H_{25}NO_2Si$: C, 69.68; H, 7.69; N, 4.28. Found: C, 69.74; H, 7.65; N, 4.22. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 19/1, flow rate = 0.8 mL/min) t_R = 9.58 min (major, *R*), t_R = 10.24 min (minor, *S*).

4.10. (*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-(4-methoxy-naphthalen-2-yl)-acetonitrile 4b

δ_H: 0.1 (s, 3H), 0.15 (s, 3H), 0.9 (s, 9H), 4.02 (s, 3H), 5.95 (s, 1H, C*H*–CN), 6.8 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.5–7.6 (m, 3H, Ar-*H*), 8.1–8.4 (m, 2H, Ar-*H*). δ_C: −5.01, −4.97, 18.19, 25.55, 55.63, 63.27, 102.63, 119.43, 122.89, 123.23, 123.78, 124.22, 125.66, 126.07, 127.42, 130.96, 156.92. Elemental Anal. Calcd for $C_{19}H_{25}NO_2Si$: C, 69.68; H, 7.69; N, 4.28. Found: C, 69.69; H, 7.63; N, 4.21. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 19/1, flow rate = 0.8 mL/min) t_R = 10.5 min (major, *R*), t_R = 11.68 min (minor, *S*).

4.11. Anthracen-9-yl-(*tert*-butyl-dimethyl-silanyloxy)-acetonitrile 5b

Spectroscopic data are in agreement as reported in the literature.[7]

Elemental Anal. Calcd for $C_{22}H_{25}NOSi$: C, 76.03; H, 7.25; N, 4.03. Found: C, 76.09; H, 7.23; N, 4.11.

4.12. 4.11.(*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-{4-[6-(*tert*-butyl-dimethyl-silanyloxymethyl)-pyridin-2-yl]-phenyl}-acetonitrile 6b

δ_H: 0.15 (s, 12H), 0.92 (s, 9H), 0.99 (s, 9H), 4.91 (s, 2H), 5.56 (s, 1H, C*H*–CN), 7.5–7.6 (m, 4H, Ar-*H*), 7.7 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 8.0 (d, *J* = 8.0 Hz, 2H, Ar-*H*). δ_C: −5.30, −5.24, −5.12, −5.03, 18.21, 18.42, 25.56, 25.97, 63.88, 66.32, 118.77, 119.16, 126.55, 127.55, 136.9, 137.43, 140.59, 155.45, 161.63. Elemental Anal. Calcd for $C_{26}H_{40}N_2O_2Si_2$: C, 66.62; H, 8.60; N, 5.98. Found: C, 66.69; H, 8.63; N, 5.91. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 49/1, flow rate = 0.5 mL/min) t_R = 9.08 min (major, *R*), t_R = 10.07 min (minor, *S*).

4.13. (*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-(4-pyridin-4-yl-phenyl)-acetonitrile 7b

δ_H: 0.18 (s, 3H), 0.25 (s, 3H), 0.95 (s, 9H), 5.58 (s, 1H, C*H*–CN), 7.5 (d, *J* = 5.6 Hz, 2H, Ar-*H*), 7.59 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.68 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 8.67 (d, *J* = 5.2 Hz, 2H, Ar-*H*). δ_C: −5.22, −5.09, 18.14, 25.48, 63.55, 118.96, 121.59, 126.78, 127.54, 137.28, 139.08, 147.38, 150.26. Elemental Anal. Calcd for $C_{19}H_{24}N_2OSi$: C, 70.33; H, 7.45; N, 8.63. Found: C, 70.39; H, 7.43; N, 8.71. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 49/1, flow rate = 0.8 mL/min) t_R = 25.8 min (major, *R*), t_R = 27.44 min (minor, *S*).

4.14. (*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-(4-pyrimidin-5-yl-phenyl)-acetonitrile 8b

δ_H: 0.19 (s, 3H), 0.26 (s, 3H), 0.96 (s, 9H), 5.58 (s, 1H, C*H*–CN), 7.64 (s, 4H, Ar-*H*), 8.96 (s, 2H, Ar-*H*), 9.23 (s, 1H, Ar-*H*). δ_C: −5.24, −5.09, 18.14, 25.47, 63.48, 118.86, 127.08, 127.53, 133.49, 135.21, 137.35, 154.88, 157.75. Elemental Anal. Calcd for $C_{18}H_{23}N_3OSi$: C, 66.42; H, 7.12; N, 12.91. Found: C, 66.39; H, 7.13; N, 12.79. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 0.8 mL/min) t_R = 28.97 min (major, *R*), t_R = 32.18 min (minor, *S*).

4.15. (*R*)-(*tert*-Butyl-dimethyl-silanyloxy)-{3-[4-(1,1,2,2-tetramethyl-propylsilanyl)-piperazin-1-yl]-phenyl}-acetonitrile

δ_H: 0.1–0.2 (s, 12H), 0.92 (s, 9H), 0.96 (s, 9H), 2.82 (s, 4H), 3.58 (s, 4H), 5.56 (s, 1H, C*H*–CN), 6.5–7.1 (m, 4H, Ar-*H*). δ_C: −5.32, −5.21, −5.14, −5.06, 18.68, 18.82, 25.36, 25.77, 48.67, 59.85, 63.75, 114.6, 116.26, 118.83, 119.32, 127.32, 132.45, 142.62. Elemental Anal. Calcd for $C_{24}H_{43}N_3OSi_2$: C, 64.66; H, 9.72; N, 9.43. Found: C, 64.64; H, 9.83; N, 9.49. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1 mL/min) t_R = 30.12 min (major, *R*), t_R = 36.48 min (minor, *S*).

4.16. (*R*)-4-{4-[(*tert*-Butyl-dimethyl-silanyloxy)-cyano-methyl]-phenoxy}-benzonitrile 10b

δ_H: 0.17 (s, 3H), 0.25 (s, 3H, 0.98 (s, 9H), 5.52 (s, 1H, C*H*–CN), 7.02 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.1 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.5 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.62 (d, *J* = 8.8 Hz, 2H, Ar-*H*). δ_C: −5.15, −5.03, 18.19, 25.55, 63.44, 106.56, 118.42, 119.08, 120.53, 128.14, 133.23, 134.27, 155.79, 160.99. Elemental Anal. Calcd for $C_{21}H_{24}N_2O_2Si$: C, 69.20; H, 6.64; N, 7.68. Found: C, 69.29; H, 6.67; N, 7.78. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 49/1, flow rate = 1 mL/min) t_R = 25.16 min (major, *R*), t_R = 27.79 min (minor, *S*).

4.17. (*R*)-2-Hydroxy-2-(3-phenoxy-phenyl)-acetonitrile

δ_H: 7.38 (m, 3H, Ar-*H*), 7.2 (m, 1H, Ar-*H*), 7.16 (m, 2H, Ar-*H*), 7.0 (m, 3H, Ar-*H*), 5.48 (s, 1H, C*H*–CN). δ_C: 158.0, 156.3, 137.0, 130.5, 129.9, 123.9, 120.9, 119.6, 119.2, 118.6, 116.7, 62.9. Elemental Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.56; H, 4.87; N, 6.28. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1 mL/min) t_R = 25.4 min (major, *R*), t_R = 33.0 min (minor, *S*).

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